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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/531,853	04/18/2005	Gilda De Luca	206,953	3983

38137 7590 06/10/2009

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EXAMINER	
KRISHNAN, GANAPATHY	
ART UNIT	PAPER NUMBER
1623	

MAIL DATE	DELIVERY MODE
06/10/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/531,853	DE LUCA ET AL.	
	Examiner	Art Unit	
	Ganapathy Krishnan	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31,34-45,55-75 and 79-86* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-31,34-45,55-75 and 79-86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A Request for Continued Examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed 3/17/2009 has been entered.

The Request for Continued Examination filed 3/17/2009 has been carefully considered. The following information provided in the amendment affects the instant application:

1. Claims 32-33, 46-54 and 76-78 have been canceled.

2. New Claims 80-86 have been added.

3. Claims 37-38, 55, 58-59, 68, 70 and 79 have been amended.

4. Remarks drawn to rejections under 35 USC 103(a) of record in the previous Office action.

Claims 1-31, 34-45, 55-75 and 79-86 are pending in the case.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-31, 34-45, 55-75 and 79-86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Luo et al (Bioconjugate Chem. 1999, 10, 755-763; document AR cited in IDS of Oct. 03, 2005) in view of Sparer et al (Controlled Release Delivery Systems, Chapter 6, 1983, 107-119; document AS cited in IDS of Oct. 03, 2005), Li et al (US 5,977,163), Desai et al (US 5,648,506; document AC cited in the IDS of Oct. 03, 2005), all of record.

Luo et al, drawn to bioconjugates, teach conjugates of hyaluronic acid wherein the carboxyl group of the hyaluronic acid is covalently bonded to a linker via an amide linkage to Taxol (Figure 2, page 756). Such conjugates showed selective toxicity towards human cancer cell lines that overexpress hyaluronic acid receptors like CD44 and RHAMM and the conjugates

showed no toxicity (page 755, abstract, right column, last paragraph). In addition to this, conjugation of anticancer and antitumor drugs to biopolymers provides advantages in drug stabilization, solubilization, localization and controlled release (page 756, right column, below figure 4).

In Figure 2 (page 756), Luo teaches the process for attachment of Taxol to hyaluronic acid wherein the carboxyl of the hyaluronic acid is attached to the spacer via an amide linkage on one end and the other end of the spacer is attached to the hydroxyl of the Taxol via an ester bond. However, the conjugate of Luo comprises hyaluronic acid conjugated to Taxol via a spacer that is a dihydrazide, which is excluded by the proviso in instant claim 1. But one of skill in the art reading Luo's teaching will realize the importance of the conjugate of Taxol and hyaluronic acid since Luo teaches that in addition to advantages with respect to drug stabilization, solubilization and controlled release of the conjugated drug, it has the advantage of hyaluronic acid as the carrier, which is immunoneutral, biocompatible and biodegradable and has been used as a vehicle and angiostatic agent in cancer therapy (page 755, introduction). Moreover, CD44 and RHAMM that are overexpressed in cancer cells are receptors for hyaluronic acid (page 756, right column, see text below figure 4). This means that a conjugate of Taxol (Taxol shows activity against several cancers) and hyaluronic acid, which is biocompatible and has antiinflammtory properties, will show selectivity towards cancer cells and thus would have optimal beneficial effects.

Sparer et al, drawn to polysaccharide-drug complexes, teaches glycosaminoglycans including hyaluronic acid are drug carriers because of their favorable properties and have various functional groups available for forming different types of bonds with drugs (page 108, line 1

through page 109, line 3). Sparer reports especially the performance of amide and ester linked glycosaminoglycan drug complexes (page 109, 4-7), which are prepared via standard coupling reaction of the carboxyl group of the hyaluronic acid to the hydroxyl and the amino group of the drug (page 112). The process for the formation of an ester linkage involves activation of the hydroxyl by dicyclohexyl carbodiimide (page 109, Experimental and page 110, last paragraph).

According to Sparer's study the release rate from amide complexes was slower and gave a prolonged constant release of the drug. According to Sparer, it would be ideal to obtain zero order release rate in all cases and still be able to vary the rate of release to fit the dosage regimen and this may be possible by selecting a given polymer drug bond and that his studies provide a base from which to design a drug release system. The rate of release may in principle be engineered by the judicious choice of drug-glycosaminoglycan bond based on the hydrolytic stability of the bond (page 117, last paragraph). This means that drug-glycosaminoglycan complexes containing bonds other than amide and ester may be important in controlled release and should be made and studied with respect to their hydrolysis. Even though Sparer does not teach a complex of glycosaminoglycans with Taxol, one of skill in the art will recognize from his teaching that the same could be done using hyaluronic acid and Taxol since both have several functional groups and different types of bonds could be formed between the two molecules with and without a spacer.

However, Luo and Sparer do not teach taxane conjugates, compositions, medical devices coated with the taxane compositions and a method of treating auto immune diseases as instantly claimed.

Li et al, drawn to Taxol complexes, teaches water-soluble complexes of paclitaxel and docetaxel with polyethylene glycol polymers (col. 1, lines 5-14). Their complexes are effective against cancers (col. 5, lines 13-18) and arthritis (col. 5, lines 43-65), and also useful for inhibiting restenosis and coating medical devices like stents (col. 5, line 66 through col. 6, line 43). According to Li such complexes improve the efficacy of anticancer therapy by providing water-soluble and controlled release paclitaxel derived compositions and also eliminate the need for solvents that are associated with side effects (col. 8, lines 34-41). The complexes could be made into compositions comprising excipients and diluents and can be made for different forms of administration. Specific antibacterial and antifungal agents could be added for preservation against microorganisms (col. 10, line 1 through 66). However, Li et al do not teach Taxol hyaluronic acid complexes. But from their teaching one of skill in the art would recognize the use of such complexes in a method of treatment of cancers, tumors and restenosis and for coating medical devices.

Desai, drawn to Taxol-carrier conjugates, teaches a process for the attachment of Taxol to carriers via different types of covalent linkages like ester, urethane, amide, amine and ether etc. (col. 4, lines 19-36 and examples 1-5). Even though Desai et al do not exemplify such conjugates using Taxol and hyaluronic acid as instantly claimed, one of skill in the art will recognize from the teaching of Desai and that of Sparer that the same type of process steps can be used for making Taxol-hyaluronic acid conjugates comprising different types of linkages as instantly claimed.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a taxane covalently bonded to hyaluronic acid optionally using a spacer, and

use them in a method of treatment and as a coating for medical devices since closely analogous complexes comprising the active agents and their use in treating cancer, restenosis and as coating for medical devices is seen to be taught in the prior art. One of ordinary skill in the art would also use different spacers in order to look for optimal beneficial effects.

One of skill in the art would be motivated to make the complexes as instantly claimed via the process as instantly claimed and use them in a method of treatment as instantly claimed and in coating medical devices since Taxol and hyaluronic acid have many functional groups which makes it possible to make complexes via different type of bonds, which according to Sparer could lead to drug complexes with varied release times, which in turn would extend the duration of treatment. Complexation with hyaluronic acid has the advantage of biocompatibility and also selectivity to cancer cells because of the overexpression of receptors (CD44) of hyaluronic acid by these cells. The presence of several functional groups in both the agents also helps to make different types of bonds that link both the agents to each other with and without a spacer.

Response to Applicants Arguments

Applicants have traversed the rejection of record made earlier arguing that:

1. The results for IC50 provided for entry 3 for HCT-116 (colon cancer cell lines) in Table 3 of Luo et al shows that the Taxol conjugate of Luo is five fold less effective than free Taxol. One of skill in the art confronted with this result would not have considered the same promising and would not have found any motivation to undertake research in the direction of the claimed invention. The conjugates of the instant invention have activity higher than that of free Taxol.

2. The conjugates of the instant invention are water soluble whereas prior art states that solubility decreases with increasing molecular weight. Luo teaches that only lower molecular weight hyaluronic acids would be cleared by the kidney and only these would be rapidly taken up by cells. The conjugates of the instant invention show very high effectiveness and also good solubility even when a HA of 200,000 Da is selected and even if a high Taxol loading is present.

3. The rest of the secondary references, Sparer, Li and Desai do not teach or suggest a conjugate of Taxol and hyaluronic acid as instantly claimed.

Applicants' arguments have been considered but are not found to be persuasive.

Applicants are pointing out to the results for just one type of cell line (HCT-116 colon cancer cell lines) in Luo and arguing that compared to this particular result their conjugates are superior. Applicants have carried out their tests on human breast adenocarcinoma cells, which are different. Applicants' conjugates have an ester linkage, whereas Luo's conjugates have an amide link. Luo shows results for three different cancer cell lines (SK-OV-3: ovary adenocarcinoma; HBL-100: human breast cancer: HCT-116: colon cancer). Perusal of results shown in Table 3 of Luo shows that the Taxol equivalents are different for different cell lines and different preparations. One of ordinary skill in the art would expect such results and hence would look for other conjugates that are more active than the ones taught by Luo. Luo also teaches that their results support the notion that increased cytotoxicity of HA-Taxol conjugate requires cellular uptake of the complex followed by hydrolytic release of the active Taxol by cleavage of the labile 2'-ester linkage (page 761, right column, see second full paragraph). The Taxol-HA conjugate shown in Figure 2 of Luo (page 756) has an ester linkage on the side of the spacer bound to the Taxol. Tis is the one that gets hydrolyzed to release the free Taxol into the

cancer cells. One of ordinary skill in the art, based on this teaching of Luo will expect a conjugate of Taxol and HA linked via an ester bond to be more active and hence would look for such conjugates as instantly claimed. One would also look for other types of linkages (based on the teaching of the secondary references, Sparer and Desai) that may be better than the ester linkage suggested by Luo.

Luo just states that low molecular weight hyaluronic acid can be cleared by the kidney. Even though Luo has used hyaluronic acid with a molecular weight of about 12,000, there is no teaching of the molecular weight cutoff for this clearance. This means that the artisan can vary the molecular weight for optimization purposes. According to Luo's teaching (page 761, right column, last paragraph though page 762 right column) cytotoxicity depends on a balance between minimal hyaluronic acid modification and maximal Taxol loading. This is a suggestion for adjustment of the percentage of Taxol loading especially if the molecular weight of hyaluronic acid is increased, i.e., more repeat units are added to the HA chain.

Sparer, Li and Desai teach are al relevant in that they teach drug release studies form conjugates (Sparer refers to conjugates of glycosaminoglycans, one of which is hyaluronic acid), taxol conjugates having different linkages and the use of related taxol conjugates for coating medical devices. Since Luo teaches the use of closely related Taxol conjugates ad their anticancer activities, the secondary references need not teach or suggest the same. The skilled artisan can take the suggestion in the secondary references and apply them to Luo's teaching for modification purposes. This is well within the skill level of the artisan. Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the

references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988 and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). Teaching, suggestion and motivation along with a reasonable expectation of success for the instant invention is seen in the prior art.

Conclusion

Claims 1-31, 34-45, 55-75 and 79-86 are rejected

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathy Krishnan whose telephone number is 571-272-0654. The examiner can normally be reached on 8.30am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ganapathy Krishnan/
Examiner, Art Unit 1623

/Shaojia Anna Jiang/
Supervisory Patent Examiner, Art Unit 1623